Hyperthyroidism (primary)

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ABSTRACT

INTRODUCTION: Hyperthyroidism is characterised by high levels of serum thyroxine and triiodothyronine, and low levels of thyroid-stimulating hormone. The main causes of hyperthyroidism are Graves' disease, toxic multinodular goitre, and toxic adenoma. About 20 times more women than men have hyperthyroidism. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments for primary hyperthyroidism? What are the effects of surgical treatments for primary hyperthyroidism? What are the effects of treatments for subclinical hyperthyroidism? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 15 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding thyroxine to antithyroid drugs (carbimazole, propylthiouracil, and thiamazole), antithyroid drugs (carbimazole, propylthiouracil, and thiamazole), radioactive iodine, and thyroidectomy.

QUESTIONS

INTERVENTIONS

DRUG TREATMENTS FOR PRIMARY HYPERTHYROIDISM

Likely to be beneficial

Unlikely to be beneficial

SURGICAL TREATMENTS FOR PRIMARY HYPERTHYROIDISM

Likely to be beneficial

TREATMENTS FOR SUBCLINICAL HYPERTHYROIDISM

Likely to be beneficial

Footnote

*Based on consensus, as RCTs would be considered unethical.

Key points

- Hyperthyroidism is characterised by high levels of serum thyroxine and triiodothyronine, and low levels of thyroid-stimulating hormone (TSH).
  - Thyrotoxicosis is the clinical effect of high levels of thyroid hormones, whether or not the thyroid gland is the primary source.
  - The main causes of hyperthyroidism are Graves' disease, toxic multinodular goitre, and toxic adenoma.
  - About 20 times more women than men have hyperthyroidism.
- There is consensus that antithyroid drugs (carbimazole, propylthiouracil, and thiamazole) are effective in treating hyperthyroidism, although we found no evidence comparing them with placebo or with each other.
  - We found no evidence that antithyroid drugs plus thyroxine (block-replace regimens) improved relapse rates compared with titration regimens.
  - Higher-dose antithyroid drugs work better when taken for longer (greater than 18 months) than for a shorter time (6 months).
  - The doses of antithyroid drugs reported in the studies we found are higher than are generally used in practice.
- There is also consensus that radioactive iodine (radioiodine) is effective for hyperthyroidism.
  - We don't know whether radioactive iodine increases risk of thyroid and extrathyroid cancer.
  - Radioactive iodine can worsen ophthalmopathy in people with Graves' disease.

Giving antithyroid drugs to people having radioiodine may increase the proportion of people with persistent or recurrent hyperthyroidism or who need further treatment.

- There is consensus that thyroidectomy is effective for hyperthyroidism.

  Total thyroidectomy is more effective than subtotal thyroidectomy for hyperthyroidism.

  Replacement thyroxine will need to be given to people who become hypothyroid after thyroidectomy.

- There may be some improvement in bone mineral density and TSH levels after treatment with antithyroid treatment in women who have subclinical hyperthyroidism.

DEFINITION

Hyperthyroidism is characterised by high levels of serum thyroxine (T4), high levels of serum triiodothyronine (T3), or both, and low levels of thyroid-stimulating hormone (TSH, also known as thyrotropin). Subclinical hyperthyroidism is characterised by decreased levels of TSH (<0.1 mU/L) but with levels of T4 and T3 within the normal range (total T4: 60–140 nanomol/L; total T3: 1.0–2.5 nanomol/L, depending on assay type). [1] The terms hyperthyroidism and thyrotoxicosis are often used synonymously; however, they refer to slightly different conditions. Hyperthyroidism refers to overactivity of the thyroid gland leading to excessive production of thyroid hormones. Thyrotoxicosis refers to the clinical effects of unbound thyroid hormones, whether or not the thyroid gland is the primary source. [2] Secondary hyperthyroidism due to pituitary adenomas, thyroiditis, iodine-induced hyperthyroiditis, and treatment of children and pregnant or lactating women are not covered in this review. Hyperthyroidism can be caused by Graves' disease (diffusely enlarged thyroid gland on palpation, ophthalmopathy, and dermopathy), toxic multinodular goitre (thyrotoxicosis and increased radioiodine uptake with multinodular goitre on palpation), or toxic adenoma (benign hyperfunctioning thyroid neoplasm presenting as a solitary thyroid nodule). [1] We have not included treatment of Graves' ophthalmopathy in this review, although we do report on worsening of Graves' ophthalmopathy with radioiodine. We have also not included euthyroid sick syndrome (a condition seen in people with, for example, pneumonia, MI, cancer, and depression — it is characterised by low levels of TSH and T3). **Diagnosis:** The diagnosis of hyperthyroidism is established by a raised serum total or free T4 or T3 hormone levels, reduced TSH level, and high radioiodine uptake in the thyroid gland along with features of thyrotoxicosis. The usual symptoms are irritability, heat intolerance and excessive sweating, palpitations, weight loss with increased appetite, increased bowel frequency, and oligomenorrhoea. People with hyperthyroidism also often have tachycardia, fine tremors, warm and moist skin, muscle weakness, and eyelid retraction or lag. [1]

INCIDENCE/ PREVALENCE

Hyperthyroidism is more common in women than in men. One study (2779 people in the UK, median age 58 years, 20 years' follow-up) found an incidence of clinical hyperthyroidism of 0.8/1000 women a year (95% CI 0.5/1000 women/year to 1.4/1000 women/year). [3] The study reported that the incidence was negligible in men. The incidence of hyperthyroidism is higher in areas of low iodine intake than in areas with high iodine intake, because suboptimal iodine intake induces nodular goitre, and, by time the nodules become autonomic, hyperthyroidism develops. [4] In Denmark, an area characterised by moderate iodine insufficiency, the overall incidence of hyperthyroidism (defined as low levels of TSH) is 9.7%, compared with 1.0% in Iceland, an area of high iodine intake. The prevalence in this Danish study was 38.7/100,000 a year in women and 2/100,000 a year in men. [5]

AETIOLOGY/ RISK FACTORS

Smoking is a risk factor, with an increased risk of both Graves' disease (OR 2.5, 95% CI 1.8 to 3.5) and toxic nodular goitre (OR 1.7, 95% CI 1.1 to 2.5). [6] In areas with high iodine intake, Graves' disease is the major cause, whereas, in areas of low iodine intake, the major cause is nodular goitre. [5] A correlation between diabetes mellitus and thyroid dysfunction has been described. In a Scottish population with diabetes, the overall prevalence of thyroid disease was found to be 13%, highest in women with type 1 diabetes (31%). As a result of screening, new thyroid disease was diagnosed in 7% of people with diabetes (hyperthyroidism in 1%). [7]

PROGNOSIS

Clinical hyperthyroidism can be complicated by severe cardiovascular or neuropsychiatry manifestations requiring admission to hospital or urgent treatment. **Mortality:** One population-based 10-year cohort study of 1191 people aged 60 years and over found a higher mortality among people who had a low initial TSH level. The excess in mortality was attributable to CVD. However, the people in this study who had a low TSH level may have had a higher prevalence of other illnesses, and adjustment was done only for age and sex, not for comorbidity. [8] We found another population-based study evaluating 3888 people with hyperthyroidism. No increase was found in all-cause mortality or serious vascular events in people whose hyperthyroidism was treated and stabilised, but an increased risk of dysrhythmias was found in people treated for hyperthyroidism compared with standard population (standardised incidence ratio 2.71, 95% CI 1.63 to 4.24). [9] **Atrial fibrillation in people with overt hyperthyroidism:** We found one cohort study evaluating the incidence of atrial fibrillation in people aged >60 years with low serum TSH concentrations (up to 0.1 mU/L). It found that low serum TSH concentrations were associated with an increased risk of atrial fibrillation

(diagnosed by ECG) at 10 years (61 people with low TSH, 1576 people with normal TSH; incidence of atrial fibrillation: 28/1000 person-years with low TSH values *v* 11/1000 person-years with normal TSH values; 13/61 [21%] with low TSH values *v* 133/1576 [8%] with normal TSH values; RR 2.53, 95% CI 1.52 to 4.20; RR calculated by *Clinical Evidence*). [10] A population-based study including 40,628 people diagnosed with hyperthyroidism in Denmark from 1977 to 1999 found that 8.3% were diagnosed with atrial fibrillation or flutter within ±30 days from the date of diagnosis of hyperthyroidism. [11] **Quality of life:** Left untreated, thyroid problems can adversely effect quality of life in many ways, which can continue in the long term. In a long-term follow-up (179 people, treated for 14–21 years before investigation), people with Graves' disease, compared with a large Swedish reference population, had diminished vital and mental quality-of-life aspects even after years of treatment. [12] **Fracture rate and bone mineral density (BMD):** Hip and spine BMD levels can decrease if hyperthyroidism is untreated. [13] However, when treated, BMD can increase to normal levels. The risk of hip fracture is also higher in people with hyperthyroidism. Progression from subclinical to overt hyperthyroidism is seen in people with nodular goitre, but not in people found by screening to be without other signs of thyroid disease. [14] A meta-analysis (search date 1996) based on data from screening studies estimated that each year 1.5% of women and 1.0% of men who had a low TSH level and normal free T4 and T3 levels developed an elevated free T4 or free T3 level. [14] Ophthalmopathy is a complication of Graves' hyperthyroidism. Treatment can be problematic and usually involves topical corticosteroids and external radiation of the eye muscles. **Thyroid volume and the nodularity of the gland influence the cure rate of hyperthyroidism:** In a controlled study (124 people with newly diagnosed hyperthyroidism), remission rates were calculated after treatment with a combined antithyroid drug plus T4 for about 2 years. People with Graves' disease with no goitre or a small goitre had a significantly better outcome compared with people with Graves' disease with a medium-sized or large goitre. Most people with multinodular goitre had a relapse within the first year after stopping medication. [15]

AIMS OF INTERVENTION

To eliminate the symptoms of hyperthyroidism and maximise quality of life, with minimum adverse effects of treatment.

OUTCOMES

Treatment success (levels of T4, T3, TSH); **relapse; changes in thyroid function** (including change of state from hyperthyroid to euthyroid/hypothyroid); **quality of life** and **neuropsychological impairments** (evaluated by cognitive function tests, memory tests, reaction time, self-rating mood scales, and depression scores); **CVD** (episodes of atrial fibrillation and ischaemic events); cardiac function (evaluated by echocardiography); changes in body composition (obesity and BMD measured by osteodensitometry or bioimpedance); prevention of progression from subclinical to overt hyperthyroidism; **adverse effects of treatments** (bone mass, fracture rate, development of hyperparathyroidism); **ophthalmopathy**.

METHODS

Clinical Evidence search and appraisal February 2010. The following databases were used to identify studies for this review: Medline 1966 to February 2010, Embase 1980 to February 2010, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2010, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study-design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing >20 individuals, no lower percentage of individuals followed up, but a minimum length of follow-up of 12 months. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We also searched for prospective cohort studies with a control group for the question on surgical treatments, and did a specific harms search for thyroid ophthalmopathy worsened by radioiodine or surgery. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 28). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of drug treatments for primary hyperthyroidism?

OPTION ANTITHYROID DRUGS (CARBIMAZOLE, PROPYLTHIOURACIL, AND THIAMAZOLE) FOR PRIMARY HYPERTHYROIDISM

- For GRADE evaluation of interventions for Hyperthyroidism (primary), see table, p 28 .
- We found no direct information from RCTs about whether antithyroid drug treatment is better than no active treatment in people with hyperthyroidism, as conducting an RCT would be unethical; there is consensus that treatment is beneficial.
- There is consensus that antithyroid drugs (carbimazole, propylthiouracil, and thiamazole) are effective in treating hyperthyroidism, although we found no evidence comparing them with placebo or with each other.
- Higher-dose antithyroid drugs work better when taken for longer (greater than 18 months) than for a shorter time (6 months).
- The doses of antithyroid drugs reported in the studies we found are higher than are generally used in practice.

Benefits and harms

Antithyroid drugs versus placebo:

We found no RCTs comparing carbimazole, thiamazole, or propylthiouracil with placebo in people with hyperthyroidism (see comment below).

Antithyroid drugs versus each other:

We found no systematic review or RCTs. We found one systematic review (search date 2009) that assessed duration of treatment and provided an indirect analysis of skin adverse effects in people taking carbimazole and thiamazole. [16] We also found one cohort study assessing agranulocytosis. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rash					
[16] Systematic review	1436 people taking carbimazole or thiamazole; number of RCTs not reported	**Proportion of people with rash** 49/722 (7%) with carbimazole No data with baseline The review did not report on hypothyroidism	Significance not assessed		
[16] Systematic review	1436 people taking carbimazole or thiamazole; number of RCTs not reported	**Proportion of people with rash** 82/714 (11%) with thiamazole No data with baseline The review did not report on hypothyroidism	Significance not assessed		
Agranulocytosis					
[17] Cohort study	30,808 people taking thiamazole or propylthiouracil Retrospective study	**Proportion of people with agranulocytosis** 93/26,435 (0.35%) with thiamazole 16/4373 (0.37%) with propylthiouracil	Significance not assessed		

Antithyroid drugs versus radioactive iodine or surgery:

We found no systematic review or RCTs.

Different durations of antithyroid treatment versus each other:

We found one systematic review (search date 2009, 4 RCTs, 390 people with Graves' hyperthyroidism). [16]

Relapse rates

Different durations of antithyroid treatments Treatment for 18 months with higher doses of carbimazole in people with Graves' hyperthyroidism may be more effective than 6 months' treatment at reducing the proportion of people who relapse over up to 18 months' treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[16] Systematic review	94 people with Graves' hyperthyroidism Data from 1 RCT	**Proportion of people relapsing, over 6-18 months' treatment** 17/46 (37%) with carbimazole 60 mg daily for 18 months 28/48 (58%) with carbimazole 60 mg daily for 6 months The review did not define relapse	OR 0.42 95% CI 0.18 to 0.96	●●○	carbimazole 60 mg daily for 18 months
[16] Systematic review	186 people with Graves' hyperthyroidism 2 RCTs in this analysis	**Proportion of people relapsing, over 12-18 months' treatment** 38/86 (44%) with carbimazole 30 mg to 50 mg daily for >18 months 50/100 (50%) with carbimazole 30 mg to 50 mg daily for 12 to 18 months The review did not define relapse	OR 0.75 95% CI 0.39 to 1.43	⟷	Not significant

Treatment success

No data from the following reference on this outcome. [16]

Changes in thyroid function

No data from the following reference on this outcome. [16]

Quality of life

No data from the following reference on this outcome. [16]

Neuropsychological impairments

No data from the following reference on this outcome. [16]

CVD

No data from the following reference on this outcome. [16]

Ophthalmopathy

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Different doses of antithyroid treatment versus each other:
We found no systematic review. We found one RCT. [18]

Relapse rates

High doses compared with low doses High doses of thiamazole may be no more effective at 12 months at reducing the proportion of people who relapse (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[18] RCT	509 people with Graves' hyperthyroidism	**Proportion of people relapsing, 12 months** 36% with thiamazole 10 mg daily 37% with thiamazole 40 mg daily Absolute numbers not reported 309 (61%) people completed the trial and were included in the analysis	P value not reported Reported as not significant	⟷	Not significant

Changes in thyroid function

Different doses of antithyroid treatment We don't know whether higher doses (40 mg/day) of thiamazole are more effective than lower doses (10 mg/day) at increasing the proportion of people who are euthyroid at 3 or 6 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change from hyperthyroid to euthyroid					
[18] RCT	509 people with Graves' hyperthyroidism	**Proportion of people euthyroid, 3 weeks** 68% with thiamazole 10 mg daily 83% with thiamazole 40 mg daily Absolute numbers not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		309 (61%) people completed the trial and were included in the analysis			
[18] RCT	509 people with Graves' hyperthyroidism	**Proportion of people euthyroid, 6 weeks** 85% with thiamazole 10 mg daily 92% with thiamazole 40 mg daily Absolute numbers not reported 309 (61%) people completed the trial and were included in the analysis	Significance not assessed		

Treatment success

No data from the following reference on this outcome. [18]

Quality of life

No data from the following reference on this outcome. [18]

Neuropsychological impairments

No data from the following reference on this outcome. [18]

CVD

No data from the following reference on this outcome. [18]

Ophthalmopathy

No data from the following reference on this outcome. [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	509 people with Graves' hyperthyroidism	**Adverse effects** with thiamazole 10 mg daily with thiamazole 40 mg daily Absolute numbers not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT reported that 1/251 (0.4%) people had granulocytopenia with thiamazole 10 mg daily; 1/258 (0.4%) people had agranulocytosis with 40 mg daily; and 1/258 (0.4%) people had pancytopenia with 40 mg daily			

Antithyroid drugs alone (titration) versus antithyroid drugs plus thyroxine (block-replace):

See option on antithyroid drugs plus thyroxine, p 15 .

Further information on studies

Comment:

Placebo-controlled trials would be considered unethical. Antithyroid drugs have been used for over 50 years, and there is consensus that they are effective. Carbimazole is a pro-drug of thiamazole. There have been concerns about bone-marrow suppression, neutropenia, and agranulocytosis with antithyroid drugs. [19] Advice includes asking people taking antithyroid drugs to report infection (especially sore throat); white blood cell count at any sign of infection; and stopping antithyroid drugs if there is clinical or laboratory evidence of neutropenia. The doses of antithyroid drugs reported in the trials are higher than generally used in practice. [19]

Adverse effects One non-systematic review found that the adverse effects of thiamazole and carbimazole were dose related, whereas those of propylthiouracil were less clearly related to dose. [20] Minor adverse effects such as cutaneous reactions, arthralgia, and gastrointestinal upset occurred in about 5% of people taking antithyroid drugs. People taking antithyroid drugs can be switched from one antithyroid drug to another; however, about 50% of people unable to tolerate one drug will have adverse effects with a second drug. [20] Hepatotoxicity was seen in 0.1% to 0.2% of people. Rare adverse effects such as vasculitis, cholestasis, and hypoglycaemia have been described.

Clinical guide:

Antithyroid drug treatment is often used as first-line treatment in Graves' disease and to render euthyroidism in nodular goitre and before radioactive iodine in Graves' disease. If allergy is present, people can be switched from one antithyroid drug to another.

OPTION RADIOACTIVE IODINE FOR PRIMARY HYPERTHYROIDISM

- For GRADE evaluation of interventions for Hyperthyroidism (primary), see table, p 28 .
- We found no direct information from RCTs about whether radioactive iodine is better than no active treatment in people with hyperthyroidism, as conducting an RCT would be unethical; there is consensus that treatment is likely to be beneficial.
- We don't know whether radioactive iodine increases risk of thyroid and extrathyroid cancer.
- Radioactive iodine can worsen ophthalmopathy in people with Graves' disease.

Benefits and harms

Radioactive iodine versus placebo:

We found no systematic review or RCTs comparing radioactive iodine treatment with placebo in people with hyperthyroidism, although there is consensus that treatment is likely to be beneficial (see comment below). We found two cohort studies [21] [22] and one case series [23] assessing adverse effects.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cancer					
[21] Cohort study	10,552 people	**Gastric cancer , mean follow-up 15 years (range 0–30 years)** with therapeutic dose of radioiodine. This retrospective study calculated standard mortality rates (SMR) and found an increased risk ratio over time of gastric cancer associated with radioiodine treatment (SMR 1.41), but it found no increased total risk of cancer	P value not reported. Significance not assessed		
[22] Cohort study	7417 people treated with radioiodine for hyperthyroidism	**Cancer mortality , 72,073 person-years of follow-up** 448/7417 with radioiodine. Expected cancer deaths: 499. See further information on studies for full details	SMR 0.90. 95% CI 0.82 to 0.98	○○○	radioiodine
Transition of nodular toxic goitre to autoimmune hyperthyroidism					
[23]	649 consecutive people with nodular toxic goitre. Case series	**Proportion of people developing radioiodine-induced Graves'-like syndrome** 6/149 (4%) with radioiodine	Significance not assessed		

Radioactive iodine versus antithyroid drugs:
We found three RCTs. [24] [25] [26]

Ophthalmopathy

Compared with medical antithyroid treatment Radioactive iodine worsens ophthalmopathy in people with Graves' disease compared with medical treatment or when combined with corticosteroids or thiamazole (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Changes in ophthalmopathy					
[24] RCT **3-armed trial**	114 people with hyperthyroidism caused by Graves' disease. The remaining arm assessed surgery	**Proportion of people with worsening ophthalmopathy** 13/39 (33%) with radioiodine. 4/38 (10%) with medical antithyroid treatment. T4 substitutions were given only when biochemical hypothyroidism occurred. 77 people in this analysis	Between-group P value not reported. P = 0.02 for radioiodine *v* surgery or medical antithyroid treatment combined	○○○	medical antithyroid treatment
[25] RCT **3-armed trial**	443 people with Graves' hyperthyroidism and mild or no ophthalmopathy. The remaining arm assessed radioiodine plus corticosteroids	**Proportion of people with worsening ophthalmopathy , 2 to 6 months** 23/150 (15%) with radioiodine. 4/148 (3%) with thiamazole. 298 people in this analysis	P <0.001	○○○	thiamazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] RCT	313 people with a recent diagnosis of Graves' hyperthyroidism	**Proportion of people with thyroid-associated ophthalmopathy , 18 months** 63/163 (39%) with iodine-131 32/150 (21%) with methimazole 15 mg twice daily Early substitution with T4 was given to both groups See further information on studies for detailed treatment regimens	P <0.001	○○○	methimazole

Treatment success

No data from the following reference on this outcome. [24] [25] [26]

Relapse rates

No data from the following reference on this outcome. [24] [25] [26]

Changes in thyroid function

No data from the following reference on this outcome. [24] [25] [26]

Quality of life

No data from the following reference on this outcome. [24] [25] [26]

Neuropsychological impairments

No data from the following reference on this outcome. [24] [25] [26]

CVD

No data from the following reference on this outcome. [24] [25] [26]

Adverse effects

No data from the following reference on this outcome. [24] [25] [26]

Radioactive iodine versus surgery:

We found one RCT that reported only adverse effects. [24]

Ophthalmopathy

Compared with surgery Radioactive iodine worsens ophthalmopathy in people with Graves' disease (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ophthalmopathy					
[24] RCT **3-armed trial**	114 people with hyperthyroidism caused by Graves' disease The remaining arm assessed medical antithyroid treatment	**Proportion people with worsening ophthalmopathy** 13/39 (33%) with radioiodine 6/37 (16%) with surgery T4 substitutions were given only when biochemical hypothyroidism occurred 76 people in this analysis	Between-group P value not reported P = 0.02 for radioiodine *v* surgery or medical antithyroid treatment combined	○○○	surgery

Treatment success

No data from the following reference on this outcome. [24]

Relapse rates

No data from the following reference on this outcome. [24]

Changes in thyroid function

No data from the following reference on this outcome. [24]

Quality of life

No data from the following reference on this outcome. [24]

Neuropsychological impairments

No data from the following reference on this outcome. [24]

CVD

No data from the following reference on this outcome. [24]

Adverse effects

No data from the following reference on this outcome. [24]

Further information on studies

[22] Although the study found that observed cancer mortality was significantly less than expected cancer mortality, it found that the incidence and mortality of small-bowel and thyroid cancers was significantly greater (small bowel: 6 diagnoses observed/1.2 expected; 6 deaths observed/0.8 expected; standardised incidence ratio 4.81, 95% CI 2.16 to 10.72; SMR 7.03, 95% CI 3.16 to 15.66; thyroid: 9 diagnoses observed/2.8 expected; 5 deaths observed/1.8 expected; standardised incidence ratio 3.25, 95% CI 1.69 to 6.25; SMR 2.78, 95% CI 1.16 to 6.67).

[25] This three-armed RCT found that ophthalmopathy worsened in 0/145 (0%) people with radioiodine plus corticosteroids; P <0.001 for radioiodine *v* radioiodine plus corticosteroids. We have not completed a full search and appraisal of the combination of radioiodine plus corticosteroids.

[26] The RCT compared iodine-131 (one dose of radioactive iodine aiming for an estimated absorbed radiation dose in the thyroid gland of 120 Gy) versus medical treatment (methimazole 15 mg twice daily; at day 14, 50 micrograms of L-thyroxine was added and increased to 100 micrograms at 2 weeks; at week 6, the dose of L-thyroxine was adjusted to normalise the levels of T3 and T4 to bring TSH to <0.4 mIU/L).

Comment: A placebo-controlled trial of radioiodine in people with hyperthyroidism would be considered unethical. Several studies have evaluated the effect of different doses.

Clinical guide:
Using high doses of radioiodine induces a high percentage of cure defined as euthyroidism or hypothyroidism and low frequency of persistent hyperthyroidism. A low initial incidence of hypothyroidism will inevitably be at the expense of a rise in the proportion of people with persistent hyperthyroidism. [27] In the USA, people with hyperthyroidism are generally given a high dose of radioiodine and then thyroxine to prevent hypothyroidism. However, in Europe, a dose of radioiodine is given to cure hyperthyroidism so that the person is euthyroid.

OPTION ADDING ANTITHYROID DRUGS (CARBIMAZOLE, PROPYLTHIOURACIL, AND THIAMAZOLE) TO RADIOACTIVE IODINE TREATMENT FOR PRIMARY HYPERTHYROIDISM (LESS EFFECTIVE THAN RADIOACTIVE IODINE ALONE)

- For GRADE evaluation of interventions for Hyperthyroidism (primary), see table, p 28 .
- Giving antithyroid drugs to people having radioactive iodine may increase the proportion of people with persistent or recurrent hyperthyroidism or who need further treatment.
- Adding antithyroid drugs to radioactive iodine has been associated with lower rates of new-onset atrial fibrillation and death compared with radioactive iodine alone.

Benefits and harms

Antithyroid drugs plus radioactive iodine versus radioactive iodine alone:

We found one systematic review (search date 2006, 14 RCTs, 1306 people with hyperthyroidism) comparing radioactive iodine treatment plus antithyroid drugs versus radioactive iodine alone. [28]

Treatment success

Compared with radioactive iodine alone Adding antithyroid drugs to radioactive iodine may be less effective at decreasing the proportion of people with persistent or recurrent hyperthyroidism, or at reducing the need for further treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[28] Systematic review	1306 people 14 RCTs in this analysis	**Proportion of people with treatment failure** with antithyroid drug plus radioiodine with radioiodine alone Treatment failure defined as persistent or recurrent hyperthyroidism or need for further treatment	RR 1.28 95% CI 1.07 to 1.52 P = 0.006 Intention-to-treat analysis	●○○	radioiodine alone
[28] Systematic review	1306 people 14 RCTs in this analysis	**Proportion of people with treatment failure** with antithyroid drug plus radioiodine with radioiodine alone Absolute results not reported Treatment failure defined as persistent or recurrent hyperthyroidism or need for further treatment	RR 1.34 95% CI 0.96 to 1.88 P = 0.09 Per-protocol analysis	⟷	Not significant
[28] Systematic review	565 people 14 RCTs in this analysis Subgroup analysis	**Proportion of people with treatment failure** 77/271 (28%) with adjuvant antithyroid treatment in the week before radioiodine treatment 55/294 (19%) with radioiodine alone Treatment failure defined as persistent or recurrent hyperthyroidism or need for further treatment	RR 1.48 95% CI 1.09 to 2.00 P = 0.01	●○○	radioiodine alone
[28] Systematic review	565 people 14 RCTs in this analysis Subgroup analysis	**Proportion of people with treatment failure** 191/442 (43%) with adjuvant antithyroid treatment in the week after radioiodine treatment 116/435 (26%) with radioiodine alone Treatment failure defined as persistent or recurrent hyperthyroidism or need for further treatment	RR 1.32 95% CI 1.04 to 1.68 P = 0.03	●○○	radioiodine alone

Changes in thyroid function

Compared with radioactive iodine alone Adding antithyroid drugs to radioactive iodine (1 week after treatment) may reduce the proportion of people with hypothyroidism (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hypothyroidism					
[28] Systematic review	1306 people 14 RCTs in this analysis	**Proportion of people with hypothyroidism** with antithyroid drug plus radioiodine with radioiodine alone	RR 0.68 95% CI 0.53 to 0.87 P = 0.0006 Intention-to-treat analysis	●○○	antithyroid drug plus radioiodine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[28] Systematic review	565 people 7 RCTs in this analysis Subgroup analysis	**Proportion of people with hypothyroidism** 62/271 (23%) with adjuvant antithyroid treatment in the week before radioiodine treatment 94/253 (36%) with radioiodine alone The review stated that there was no difference in summary estimates for different antithyroid drugs	RR 0.76 95% CI 0.57 to 1.01 P = 0.06	⟷	Not significant
[28] Systematic review	875 people 9 RCTs in this analysis Subgroup analysis	**Proportion of people with hypothyroidism** 30/442 (7%) with adjuvant antithyroid treatment in the week after radioiodine treatment 64/435 (15%) with radioiodine alone Absolute numbers not reported The review stated that there was no difference in summary estimates for different antithyroid drugs	RR 0.57 95 % CI 0.41 to 0.78 P <0.001	●○○	adjuvant antithyroid treatment in the week after radioiodine treatment

CVD

Compared with radioactive iodine alone We don't know whether adding antithyroid drugs to radioactive iodine reduces the proportion of people with new-onset atrial fibrillation (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
CVD					
[28] Systematic review	1306 people 14 RCTs in this analysis	**Proportion of people with new-onset atrial fibrillation** 1/660 (0.2%) with antithyroid drugs plus radioiodine 3/646 (0.5%) with radioiodine alone	Significance not assessed		

Quality of life

No data from the following reference on this outcome. [28]

Neuropsychological impairments

No data from the following reference on this outcome. [28]

Relapse rates

No data from the following reference on this outcome. [28]

Ophthalmopathy

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[28] Systematic review	1306 people 14 RCTs in this analysis	**Mortality** 1/660 (0.2%) with antithyroid drugs plus radioiodine 6/646 (0.9%) with radioiodine alone	Significance not assessed		
Adverse effects (any)					
[28] Systematic review	660 people 14 RCTs in this analysis	**Adverse effects** 12/660 (2%) with adjuvant antithyroid drugs The review reported that adverse effects with adjuvant antithyroid drugs were mainly allergic skin reactions to thiamazole The review reported that adjuvant antithyroid drugs were associated with reduced thyroid hormone concentrations for between 7 and 12 weeks after radioiodine treatment For further data on adverse effects, also see option on antithyroid drugs, p 4	Significance not assessed		

Further information on studies

[28] The RCTs used the following antithyroid drugs, given in the week before or after radioiodine treatment: carbimazole (3 RCTs), propylthiouracil (4 RCTs), and thiamazole (6 RCTs); and one RCT had an additional treatment arm and used both propylthiouracil and thiamazole. The review reported that the quality of the methods of the included RCTs was low, with few RCTs giving enough information about randomisation or allocation concealment.

Comment: The review did not draw firm conclusions about the optimal interruption period of antithyroid drugs for the people having radioiodine treatment (to avoid both relapse of hyperthyroidism and cardiovascular complications).

Clinical guide:
In people with severe hyperthyroidism, adjuvant antithyroid treatment can be used to stabilise the person, but should be discontinued about 1 week before and after radioiodine treatment to avoid treatment failure of the radioiodine.

OPTION ANTITHYROID DRUGS (CARBIMAZOLE, PROPYLTHIOURACIL, AND THIAMAZOLE) PLUS THYROXINE FOR PRIMARY HYPERTHYROIDISM

- For GRADE evaluation of interventions for Hyperthyroidism (primary), see table, p 28 .

- Adding thyroxine to block-replace regimens of antithyroid drugs seems no more effective in reducing relapse rates at 12 to 24 months.

Benefits and harms

Antithyroid drugs plus thyroxine (block-replace) versus antithyroid drugs alone (titration):

We found one systematic review (search date 2009, 12 RCTs, 1250 people with Graves' hyperthyroidism). [16]

Relapse rates

Antithyroid drugs plus thyroxine (block-replace) compared with antithyroid drugs alone (titration) Block-replace regimens of antithyroid drugs plus thyroxine seem no more effective than titration regimens of antithyroid drugs alone in reducing the proportion of people with Graves' hyperthyroidism who relapse at 12 to 24 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[16] Systematic review	1250 people with Graves' hyperthyroidism 12 RCTs in this analysis	**Proportion of people relapsing, 12 to 24 months** 322/636 (51%) with block-replace regimen of antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) plus thyroxine or triiodothyronine 332/614 (54%) with antithyroid drugs alone (titration) The review did not define relapse	OR 0.86 95% CI 0.68 to 1.08	⟷	Not significant

Treatment success

No data from the following reference on this outcome. [16]

Changes in thyroid function

No data from the following reference on this outcome. [16]

Quality of life

No data from the following reference on this outcome. [16]

Neuropsychological impairments

No data from the following reference on this outcome. [16]

CVD

No data from the following reference on this outcome. [16]

Ophthalmopathy

No data from the following reference on this outcome. [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rash					
[16] Systematic review	1238 people with Graves' hyperthyroidism 7 RCTs in this analysis	**Proportion of people with rash , 12 to 24 months** 61/619 (10%) with block-replace regimen of antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) plus thyroxine or triiodothyronine 36/619 (5%) with antithyroid drugs alone (titration) See also harms of antithyroid drugs, p 4	OR 1.71 95% CI 1.17 to 2.69	●○○	antithyroid drugs alone (titration)
Withdrawals					
[16] Systematic review	698 people with Graves' hyperthyroidism 4 RCTs in this analysis	**Withdrawals because of adverse effects , 12 to 24 months** 58/353 (16%) with block-replace regimen of antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) plus thyroxine or triiodothyronine 30/344 (9%) with antithyroid drugs alone (titration) See also harms of antithyroid drugs, p 4	OR 2.03 95% CI 1.30 to 3.18	●●○	antithyroid drugs alone (titration)
Agranulocytosis					
[16] Systematic review	943 people with Graves' hyperthyroidism 5 RCTs in this analysis	**Proportion of people with agranulocytosis , 12 to 24 months** 9/476 (2%) with block-replace regimen of antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) plus thyroxine or triiodothyronine 3/467 (1%) with antithyroid drugs alone (titration) See also harms of antithyroid drugs, p 4	OR 2.84 95% CI 0.91 to 8.91	⟷	Not significant

Initial antithyroid drugs followed by either thyroxine or no treatment:

We found one systematic review (search date 2009, 4 RCTs, 566 people with Graves' hyperthyroidism). [16]

Relapse rates

Compared with initial antithyroid drugs followed by no treatment Initial antithyroid drugs followed by thyroxine may be no more effective at reducing relapses in people with Graves' hyperthyroidism (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[16] Systematic review	566 people with Graves' hyperthyroidism 4 RCTs in this analysis	**Proportion of people relapsing, 12 to 24 months** 88/282 (31%) with initial antithyroid drugs followed by thyroxine 82/284 (29%) with initial antithyroid drugs followed by no treatment The review did not define relapse	OR 1.15 95% CI 0.79 to 1.67 P = 0.46	⟷	Not significant

Treatment success

No data from the following reference on this outcome. [16]

Changes in thyroid function

No data from the following reference on this outcome. [16]

Quality of life

No data from the following reference on this outcome. [16]

Neuropsychological impairments

No data from the following reference on this outcome. [16]

CVD

No data from the following reference on this outcome. [16]

Ophthalmopathy

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Antithyroid drugs plus thyroxine (block-replace) versus radioactive iodine or surgery:

We found no systematic review or RCTs.

Further information on studies

Comment: In the systematic review, the doses of thiamazole used for block-replace were high (60–80 mg/day) in several of the RCTs, and thus higher than used in low-dose block-replace treatment (typically 20 mg/day). [29] This may account for the finding of more adverse effects with block-replace treatment in high-dose compared with monotherapy (low dose).

Clinical guide:
Block-replace treatment can be used if it is difficult to render euthyroidism on titration regimen.

QUESTION What are the effects of surgical treatments for primary hyperthyroidism?

OPTION THYROIDECTOMY FOR PRIMARY HYPERTHYROIDISM

- For GRADE evaluation of interventions for Hyperthyroidism (primary), see table, p 28 .
- There is consensus that thyroidectomy is effective for hyperthyroidism.
- Total thyroidectomy is more effective than subtotal thyroidectomy for hyperthyroidism.
- Replacement thyroxine will need to be given to people who become hypothyroid after thyroidectomy.

Benefits and harms

Thyroidectomy versus placebo:

We found no systematic review or RCTs comparing surgery with placebo in people with hyperthyroidism, although there is consensus that treatment is beneficial.

Thyroidectomy versus antithyroid drugs or radioactive iodine:

We found no systematic review or RCTs.

Total thyroidectomy versus subtotal thyroidectomy:

We found one systematic review (search date 1998; 35 studies [study types not reported], 7241 people with Graves' disease) [30] and one subsequent RCT. [31]

Treatment success

Compared with subtotal thyroidectomy Total thyroidectomy may be more effective at reducing the proportion of people with Graves' disease who have persistent or recurring hyperthyroidism (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[30] Systematic review	7241 people with Graves' disease Data from 35 studies; study types not reported	**Proportion of people with recurrence of hypothyroidism , 4 months to 32 years** 0% with total thyroidectomy 8% with subtotal thyroidectomy Absolute numbers not reported Analysis not by intention to treat	Significance not assessed		

No data from the following reference on this outcome. [31]

Changes in thyroid function

Compared with subtotal thyroidectomy Total thyroidectomy may be more effective at reducing the proportion of people with Graves' disease who become hypothyroid or euthyroid (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Changes in thyroid function					
[30] Systematic review	7241 people with Graves' disease Data from 35 studies; study types not reported	**Proportion of people becoming hypothyroid or euthyroid , 4 months to 32 years** 100% with total thyroidectomy 86% with subtotal thyroidectomy Absolute numbers not reported 100% of people became hypothyroid with total thyroidectomy 26% of people became hypothyroid and 60% euthyroid after subtotal thyroidectomy Analysis not by intention to treat	Significance not assessed		

No data from the following reference on this outcome. [31]

Ophthalmopathy

Total thyroidectomy compared with subtotal thyroidectomy Total thyroidectomy, bilateral subtotal thyroidectomy, and unilateral total thyroidectomy plus contralateral subtotal thyroidectomy seem equally effective at increasing the proportion of people with an improvement in Graves' ophthalmopathy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Changes in ophthalmopathy					
[31] RCT **3-armed trial**	150 people with Graves' disease Subgroup analysis	**Proportion of people with improvement in Graves' ophthalmopathy** 22/31 (71%) with total thyroidectomy 21/29 (72%) with bilateral subtotal thyroidectomy (total remnant <4 mL) 20/29 (69%) with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL)	P >0.05 among groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment 89 people in this analysis			
[31] RCT **3-armed trial**	150 people with Graves' disease Subgroup analysis	**Proportion of people with documented improvement of eye symptoms** 71% with total thyroidectomy 74% with bilateral subtotal thyroidectomy (total remnant <4 mL) 74% with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL) Absolute numbers not reported Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment 98/150 people (65%) had Graves' ophthalmopathy; 61/98 (62%) had documented improvement of eye symptoms	P >0.05 among groups	⟷	Not significant
[31] RCT **3-armed trial**	150 people with Graves' disease Subgroup analysis	**Reduction in Graves' opthalmopathy score (American Thyroid Association scale; 0 = best, 40 = worst)** –2.0 with total thyroidectomy –2.5 with bilateral subtotal thyroidectomy (total remnant <4 mL) –2.0 with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL) Absolute numbers not reported Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment 98/150 people (65%) had Graves' ophthalmopathy; see further information on studies	P >0.05 among groups	⟷	Not significant

No data from the following reference on this outcome. [30]

Relapse rates

No data from the following reference on this outcome. [30] [31]

Quality of life

No data from the following reference on this outcome. [30] [31]

Neuropsychological impairments

No data from the following reference on this outcome. [30] [31]

CVD

No data from the following reference on this outcome. [30] [31]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Permanent recurrent laryngeal nerve injury					
[30] Systematic review	7241 people with Graves' disease Data from 35 studies; study types not reported	**Proportion of people with permanent recurrent laryngeal nerve injury , 4 months to 32 years** 0.9% with total thyroidectomy 0.7% with subtotal thyroidectomy Absolute numbers not reported The review reported no perioperative mortalities from thyroid storm, no permanent recurrent laryngeal nerve palsy, and no postoperative mortalities Analysis not by intention to treat	P >0.05	⟷	Not significant
[31] RCT **3-armed trial**	150 people with Graves' disease	**Proportion of people with permanent recurrent laryngeal nerve paralysis** 1/47 (2.1%) with total thyroidectomy 0/49 (0%) with bilateral subtotal thyroidectomy (total remnant <4 mL) 1/54 (1.9%) with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL) Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment	P >0.05 among groups	⟷	Not significant
Early postoperative hypoparathyroidism					
[31] RCT **3-armed trial**	150 people with Graves' disease	**Proportion of people with early postoperative hypoparathyroidism** 14/47 (30%) with total thyroidectomy 5/49 (10%) with bilateral subtotal thyroidectomy (total remnant <4 mL) 3/54 (6%) with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL)	P = 0.002 for total thyroidectomy *v* other procedures	○○○	bilateral subtotal thyroidectomy or unilateral total thyroidectomy plus contralateral subtotal thyroidectomy

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment			
Permanent hypoparathyroidism					
[31] RCT **3-armed trial**	150 people with Graves' disease	**Proportion of people with permanent hypoparathyroidism** 5/47 (11%) with total thyroidectomy 2/49 (4%) with bilateral subtotal thyroidectomy (total remnant <4 mL) 1/54 (2%) with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL) Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment	P value not reported Reported as not significant	⟷	Not significant
Wound infection					
[31] RCT **3-armed trial**	150 people with Graves' disease	**Proportion of people with wound infection** 2/47 (4%) with total thyroidectomy 1/49 (2%) with bilateral subtotal thyroidectomy (total remnant <4 mL) 2/54 (4%) with unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant <4 mL) Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment	P value not reported Reported as not significant	⟷	Not significant

Further information on studies

[31] Postoperative endocrine ophthalmopathy was found in 5/57 (9%) people who did not have preoperative Graves' ophthalmopathy (data for each group not reported, reported as no significant difference between "total and subtotal thyroidectomy").

Comment: Placebo-controlled trials of surgery in people with hyperthyroidism would be considered unethical.

Clinical guide:
Surgery is often used for people with large goitres.

QUESTION What are the effects of treatments for subclinical hyperthyroidism?

OPTION ANTITHYROID TREATMENT FOR SUBCLINICAL HYPERTHYROIDISM

- For GRADE evaluation of interventions for Hyperthyroidism (primary), see table, p 28 .

- There may be some improvement in bone mineral density and TSH levels after treatment with antithyroid treatment in women who have subclinical hyperthyroidism.

Benefits and harms

Radioactive iodine:

We found one controlled clinical trial. [32]

Treatment success

Radioactive iodine compared with no antithyroid treatment Radioactive iodine may be more effective at 2 years at increasing TSH levels, and at lowering free T4 and T3 levels within normal ranges in postmenopausal women with no compression symptoms from nodular goitre (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[32]	28 post-menopausal women with nodular goitre Controlled clinical trial (CCT)	**TSH level , 2 years** 0.390 mU/L with radioactive iodine 0.023 mU/L with no treatment Women with compression symptoms from the goitre (16 women) were given radioactive iodine; women with no compression symptoms (12 women) were given no antithyroid treatment See further information on studies for detailed population details	P <0.001	○○○	radioactive iodine
[32]	28 post-menopausal women with nodular goitre Controlled clinical trial (CCT)	**Reduction in free T3 level , 2 years** From 2.03 arbitrary units to 1.58 arbitrary units with radioactive iodine Normal range 0.84 to 2.8 arbitrary units Women with compression symptoms from the goitre (16 women) were given radioactive iodine; women with no compression symptoms (12 women) were given no antithyroid treatment See further information on studies for population details	P <0.01	○○○	radioactive iodine
[32]	28 post-menopausal women with nodular goitre Controlled clinical trial (CCT)	**Reduction in free T4 level , 2 years** From 102 arbitrary units to 80 arbitrary units with radioactive iodine Normal range 62 to 158 arbitrary units Women with compression symptoms from the goitre (16 women) were given radioactive iodine; women with no compression symptoms (12 women) were given no antithyroid treatment See further information on studies for population details	P <0.02	○○○	radioactive iodine

CVD

Compared with no antithyroid treatment Radioactive iodine may be more effective at 2 years at increasing hip and spine bone mineral density in postmenopausal women with no compression symptoms from nodular goitre (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Bone mineral density (BMD)					
[32]	28 post-menopausal women with nodular goitre Controlled clinical trial (CCT)	**Spine BMD , 2 years** 102% of initial BMD with radioactive iodine 96% of initial BMD with no treatment Women with compression symptoms from the goitre (16 women) were given radioactive iodine; women with no compression symptoms (12 women) were given no antithyroid treatment See further information on studies for detailed population details	P <0.02	○○○	radioactive iodine
[32]	28 post-menopausal women with nodular goitre Controlled clinical trial (CCT)	**Hip BMD , 2 years** 102% of initial BMD with radioactive iodine 98% of initial BMD with no treatment Women with compression symptoms from the goitre (16 women) were given radioactive iodine; women with no compression symptoms (12 women) were given no antithyroid treatment See further information on studies for detailed population details	P <0.01	○○○	radioactive iodine

Relapse rates

No data from the following reference on this outcome. [32]

Changes in thyroid function

No data from the following reference on this outcome. [32]

Neuropsychological impairments

No data from the following reference on this outcome. [32]

Quality of life

No data from the following reference on this outcome. [32]

Ophthalmopathy

No data from the following reference on this outcome. [32]

Adverse effects

No data from the following reference on this outcome. [32]

Further information on studies

[32] Population: 28 postmenopausal women with nodular goitre with free thyroxine (T4) and triiodothyronine (T3) estimates within the normal range (range not reported) and low thyroid-stimulating hormone (TSH, also known as thyrotropin; <0.20 mU/L).

Comment: The women in the CCT were not randomised, but the indication of treatment was compression symptoms of goitre and not thyroid function or symptoms of hyperthyroidism. [32]

Clinical guide:
Theoretically, the treatment of subclinical hyperthyroidism could induce hypothyroidism; however, we found no RCT that evaluated this.

GLOSSARY

Block-replace treatment Combination of antithyroid treatment and concomitant thyroid-replacement therapy.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antithyroid drugs for primary hyperthyroidism One systematic review assessing different durations of treatment updated. [16] The review found no additional RCTs, therefore no new data were added. Categorisation unchanged (Likely to be beneficial).

Antithyroid drugs plus thyroxine for primary hyperthyroidism One systematic review updated. [16] The review did not include any additional RCTs, therefore no new data were added. Categorisation unchanged (Unlikely to be beneficial).

Radioactive iodine for primary hyperthyroidism One RCT added comparing iodine-131 versus medical treatment for 18 months. The RCT found that iodine-131 increased the risk of thyroid-associated ophthalmopathy compared with medical treatment. [26] Categorisation unchanged (Likely to be beneficial).

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Disclaimer

GRADE **Evaluation of interventions for Hyperthyroidism (primary).**

Important outcomes	Changes in thyroid function, CVD, Neuropsychological impairments, Ophthalmopathy, Quality of life, Relapse rates, Treatment success								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of drug treatments for primary hyperthyroidism?									
4 (390) [16]	Relapse rates	Different durations of antithyroid treatment versus each other	4	0	0	–2	0	Low	Consistency point deducted for different results at different end points, but added for dose response. Directness points deducted for not defining outcome and for using higher doses than would be used in practice
1 (309) [18]	Relapse rates	Different doses of antithyroid treatment versus each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for using higher doses than would normally be used in practice
1 (309) [18]	Changes in thyroid function	Different doses of antithyroid treatment versus each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for using higher doses than would normally be used in practice
3 (870) [24] [25] [26]	Ophthalmopathy	Radioactive iodine versus antithyroid drugs	4	0	0	0	0	High	
1 (114) [24]	Ophthalmopathy	Radioactive iodine versus surgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
14 (1306) [28]	Treatment success	Antithyroid drugs plus radioactive iodine versus radioactive iodine alone	4	–2	0	0	0	Low	Quality points deducted for poor methodology and uncertainty about randomisation/concealment
14 (1306) [28]	Changes in thyroid function	Antithyroid drugs plus radioactive iodine versus radioactive iodine alone	4	–2	0	0	0	Low	Quality points deducted for poor methodology and uncertainty about randomisation/concealment
14 (1306) [28]	CVD	Antithyroid drugs plus radioactive iodine versus radioactive iodine alone	4	–2	0	0	0	Low	Quality points deducted for poor methodology and uncertainty about randomisation/concealment
12 (1250) [16]	Relapse rates	Antithyroid drugs plus thyroxine (block-replace) versus antithyroid drugs alone (titration)	4	0	0	–1	0	Moderate	Directness point deducted for not defining outcome
4 (566) [16]	Relapse rates	Initial antithyroid drugs followed by either thyroxine or no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for not defining outcome
What are the effects of surgical treatments for primary hyperthyroidism?									
35 (7241) [30]	Treatment success	Total thyroidectomy versus subtotal thyroidectomy	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for no intention-to-treat analysis

Important outcomes	Changes in thyroid function, CVD, Neuropsychological impairments, Ophthalmopathy, Quality of life, Relapse rates, Treatment success								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
35 (7241) [30]	Changes in thyroid function	Total thyroidectomy versus subtotal thyroidectomy	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for no intention-to-treat analysis
1 (150) [31]	Ophthalmopathy	Total thyroidectomy versus subtotal thyroidectomy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatments for subclinical hyperthyroidism?									
1 (28) [32]	Treatment success	Radioactive iodine	2	–1	0	0	0	Very low	Quality point deducted for sparse data
1 (28) [32]	CVD	Radioactive iodine	2	–1	0	0	0	Very low	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.